GUIDELINE FOR THE ARRANGEMENT AND CONTENT OF A PREMARKET APPROVAL (PMA) APPLICATION FOR A COCHLEAR IMPLANT IN ADULTS AT LEAST 18 YEARS OF AGE

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U.S. Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health

PREFACE

This guideline is intended to aid applicants in the preparation of PMAs for cochlear implants in adults at least 18 years of age. The guideline describes the kind of information needed to allow the agency to evaluate the safety and effectiveness of these devices in adults. In addition, an appendix to the guideline provides information regarding patient informed consent and postmarket surveillance.

Previous guidances (drafts) for preparation of PMAs for cochlear implants in adults was made available in 1986 and 1988. Also available from the agency is the PMA Approval Manual which covers the arrangement and content of a PMA in detail.

Wherever possible, an application should follow the guidelines presented here and provide an explanation of any omission to avoid unnecessary questions from the Center. The submission of PMAs which contain all necessary information will expedite the review and approval of these applications.

If there are any questions or comments concerning this guideline, please contact Celeste F. Bove' or Jane Yurawecz, Division of OB-GYN, ENT and Dental Devices, Office of Device Evaluation, Center for Devices and Radiological Health (HFZ-470), Food and Drug Administration, 1390 Piccard Drive, Rockville, Maryland 20850, telephone (301) 427-1230.

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I. Cover Page

A. Name and address of applicant

B. Signature of applicant or authorized representative in the United States

C. Classification (generic) name of the device if applicable

D. Device trade name

E. Model number of the device if applicable

F. Identifying numbers of all INDs, NDAs, IDEs, PMAs, PDPs, reclassification petitions, or 510(k)s previously submitted for this device

G. Indications for use

H. Name and address of manufacturing site(s)

I. Date when manufacturing site(s) will be ready for inspection or date of latest FDA inspection

J. Environmental Impact

1. Claim of categorical exclusion

2. If no claim of categorical exclusion, include an environmental assessment

II. Table of Contents

A. Volume and page number of each item referred to in the table of contents

B. Separate sections included for nonclinical laboratory studies and clinical investigations involving human subjects

C. In at least **one** copy, identify any information believed to be trade secret or confidential commercial or financial information. Although identification of the information is required in only one copy, the confidential information must be included in **all** copies of the PMA. Submit six copies of each original PMA and three copies of each amendment or supplement. Additional copies may be requested by FDA if needed for advisory panel review.

III. Summary of Safety and Effectiveness

A. Indications for use

B. The description of the device including an explanation of how the device functions, the technique for coupling signals across or through skin to implanted components, the basic scientific concepts which form a basis for the device, the physical characteristics of the device, the contraindications for the device, the chemical identities of the materials used in the device and their potential toxicity including carcinogenicity

C. A description of alternate practices and procedures (i.e., prostheses including approved cochlear implants, or aids for the profoundly hearing impaired individual) and the relative risks and benefits of each

D. Marketing history of the device

E. Possible and/or probable adverse effects of the device

F. Summary of studies

1. Abstracts of any other data, information or report described in the PMA which relates to safety and effectiveness (21 CFR 814.20(b)(8)(ii))

2. Summaries of the results of the nonclinical laboratory studies and clinical investigations

a. Summary of the nonclinical laboratory studies

(1) parameters and length of study(ies)

(2) number of devices analyzed

b. Summary of the clinical investigations

(1) patient inclusion and exclusion criteria

(2) study population

(3) study period

(4) safety and effectiveness data

(a) a table of all investigators and number of investigational subjects

(b) nature of the study (e.g., single-blind, with repeated measures on a single subject)

(c) a table specifying the age of each subject in the study and the totals in each group

(d) a listing of each claim with a summary of the evidence for each claim (indication for use) cited in the labeling (The results by claim should be given either by combining the results of equivalent types of studies done or by citing the results of other well done studies separately and then drawing a conclusion.)

(e) an assessment of the comparability of treatment groups (e.g., categorized by prelingual, postlingual, borderline) for each relevant baseline variable or relevant combination of variables (including demographic, age, risk factors, etc.), by the use of tables, graphical presentation, and other appropriate statistical techniques

(5) the section on adverse reactions and complications with a summary table for each type of adverse reaction, side effect, injury, toxicity, carcinogenicity, or sensitivity reaction (The incidence and severity of each adverse reaction or effect should be specified and a statement included as to whether the applicant considers the adverse reaction or effect to be significant or not. The tables should include the age of each subject, and the investigator's name, with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. For each adverse reaction or effect, it should be

stated how this information is contained in the labeling, e.g., as a contraindication, warning, precaution or adverse effect).

(6) patient discontinuation

(a) explanation

(7) patient complaints

(8) device failures and replacements (i.e., how did it fail, what component failed, nature of the replacement if done, was there a cochlear reinsertion?)

(9) statistical analysis of the investigations

(10) contraindications and precautions

(11) other information as appropriate

G. Conclusions drawn from the studies

1. Discussion of valid scientific evidence (21 CFR 860.7)

2. Discussion of data on safety and effectiveness

3. Risk/benefit analysis

4. Discussion of postapproval studies or surveillance, if needed

IV. Device Characteristics and Manufacturing Section

A. Description of device including pictorial representations and an engineering description of operation at the circuit level

B. Description of each of the functional components or ingredients of the device if the device consists or more than one physical component or ingredient

1. A complete set of electrical schematics

2. Detailed drawings and descriptions of all components

3. Rationale for the design with references to relevant literature

4. Electrical specifications and, where appropriate, references to laboratory testing that established these specifications

5. Design characteristics

    a. System frequency response, referred to the input

    b. Characteristics of the stimulus (frequency, waveform, amplitude) and relationship of the stimulus to the input audio signal (i.e., What is the transfer function?)

    c. Design provisions to avoid excessive stimulation (including the effects of electromagnetic interference)

    d. Means of attachment of external connector or transmitter and the effects of hair and varying skin thickness

    e. Description of user controls and audiological equipment used in conjunction with device

    f. Active electrode(s) shape and dimensions including the thickness of the electrodes, characteristics of the electrode, dimensional tolerances, effective surface area, and resultant maximum charge density per phase.

    g. Description and implant site of reference or return electrode

6. Description of radiopacity or other means of the localization of the implanted components

C. Description of the properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition (including a statement regarding inability of patients to undergo MRI)

D. Description of the principles of operation of the device

E. Description of the methods, facilities, and controls used in the manufacture, processing, packing, storage, and installation of the device

1. The location of the manufacturing facility(ies) with the street address and other appropriate directions and the establishment registration number (if applicable)

2. A description of the organization of the firm including assignment of responsibility (see 21 CFR 820.20, 820.25)

3. A description of the physical plant(s) including environmental controls having an effect on the device (see 21 CFR 820.25, 820.40, 820.56) and an environmental assessment as required under 21 CFR 25.55 and, when requested by FDA, an environmental impact statement meeting the requirements of 21 CFR Part 25

4. A description of manufacturing equipment directly involved with production of the device (see 21 CFR 820.60, 820.61)

5. A description of the control system for components (see 21 CFR 820.80, 820.81)

6. A description, including a flow chart, of the manufacturing process and quality control procedures including standards for acceptance or rejection (see 21 CFR 820.100, 820.101, 820.115, 820.116)

    a. The manufacturing documentation of the implant unit with complete manufacturing process specifications, assembly instructions and manufacturing assembly drawings for each stage, from subassembly to final assembly, with full traceability of the product (Similar documentation should be supplied for top assembly stage of any nonimplanted system components.)

    b. Duplicate manufacturing assembly drawings under sections IV.A. and B. unless the applicable drawings are referenced (Cross references between schematics and assembly drawings should be listed if they are not given on the drawings.)

7. The details of mixing, forming and curing, including the materials, sources of the materials, and percentage composition of the materials used in the device

8. Assessment of the uniformity of the components in the completed devices and the procedures for quality control

9. A description of packaging, sterilization, and labeling controls (see 21 CFR 820.120, 820.121, 820.130) (For a sterile device, the applicant should include a description of sterilization procedures including the method of sterilization, validation, and pyrogenicity testing and results.)

10. A description of holding, distribution and installation controls (see 21 CFR 820.150, 820.151, 820.152)

11. A description of finished device inspection procedures (see 21 CFR 820.160, 820.161, 820.162)

12. A description and location of device records (see 21 CFR 820.180, 820.181, 820.182, 820.184, 820.185, 820.195 820.198)

V. Performance Standards

A. Meets section 514 performance standard (Give name of standard; justify any deviation.)

B. Meets Radiation Control for Health and Safety Act (42 U.S.C. 263) standard (Give name of standard; justify any deviation.)

C. Meets voluntary standard (Give name of standard; justify any deviation.)

VI. Technical Sections

A. Nonclinical laboratory studies: including a statement whether each nonclinical study was conducted in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies, 21 CFR Part 58 (If not, give a brief statement of the reason for the noncompliance.)

1. Microbiological

2. Toxicological

3. Immunological

4. Biocompatibility

a. Biocompatibility studies on all materials which are in direct contact with the body, especially the implanted components

b. Description of the electrode material and its electrical characteristics when in contact with tissue

5. Stress

6. Wear

a. Engineering tests performed and the results relative to material properties as well as to design and rationale

b. The physical properties of the implanted devices after prolonged exposure to the biological environment (This study should include a sufficient number of devices, one per animal, implanted into the cochlea of suitable animal models for sufficient lengths of time (i.e., time sufficient to provide reasonable confirmation of all claims about effectiveness or safety. In-vitro physiological model testing can be performed in place of an animal study provided the biocompatibilities of the materials in the implanted device have been demonstrated.)

c. The system reliability with assessment both predictively and retrospectively (Predictive techniques include tolerance analysis, fault tree analysis, failure modes and effects analysis (FMEA) and mean time between failure (MTBF) prediction. Retrospective techniques include demonstrations of reliability through environmental and accelerated stress tests as well as FMEA and fault tree analyses of actual in-vivo and in-vitro failures. Design revisions that result from the system reliability analyses should be discussed. Particular attention should be given to failures that could injure the patient, create excessive noise or discomfort, or require correctable surgery. Software system and safety should be discussed in detail.)

(1) A discussion of the techniques for predicting and testing the in-vivo reliability and stability of implanted components should be included. In this regard, the sponsor must set forth the rationale and test data that support his selection of electronic components, electrode materials, lead materials, joining methods and sealing techniques intended to prevent or retard deterioration, such as corrosion, aging, etc., of implanted circuit components.

(2) To summarize, the reliability analysis should address predictive analyses as described above with special emphasis on methods and data used in FMEA and tolerance analysis and on determination of FMEA categories, and retrospective methods as described above with special emphasis on methods and data used to evaluate in-vitro reliability of implanted components and on environmental test methods and results for nonimplanted components.

7. Shelf life

8. Other appropriate testing as necessary

a. Electrode insertion (histopathological assessment of the mechanical effects of electrode insertion into the cochleae of temporal bones of cadavers including the amount of difference in insertion of electrode in cadavers verses temporal bones)

b. Characterization of the level and duration of stimulation with evidence of the safety of these levels

c. Measurement of DC levels (including measurement of the imbalance of the biphasic charge)

d. Electromagnetic susceptibility testing

e. Electrical isolation features for percutaneous devices

f. Environmental tests (e.g., dry heat, cold temperature, hermeticity, free fall, thermal cycling, vibration impact shock, electrode weld tests, electrode stretch and flex tests, failure mode analysis)

g. Cochlear histopathology (performed on temporal bones of deceased patients when possible)

h. Animal studies in addition to the study described under VI.A.6.b. above (Include the protocol, the objective of the study, the experimental design and method of performing the study, the type and number of animals used for studies of intracutaneous irritation, systemic toxicity, intramuscular implantation, sensitization, pyrogenicity, and assessment of damage to the peripheral and central auditory systems, the time span of the studies, and in-vitro testing of cytotoxicity, hemolysis, and cell growth inhibition. Provide an analysis of the data, and a description of any modifications made on the basis of this testing.)

Include a statement whether each nonclinical study was conducted in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies, 21 CFR Part 58. If not, explain the reason for the noncompliance.

B. Clinical Investigations

The clinical investigation is intended to include a controlled clinical trial designed to demonstrate safety and effectiveness. The number of patients should be based on and support the hypotheses/claims that the sponsor wishes to test. The study must have at least two investigators at different locations each with a sufficient number of patients. These trials should monitor patients closely with 100 percent follow-up or with a detailed explanation required for any loss of follow-up. They should be conducted by investigators who are experienced with otologic middle ear surgery, aural habilitation/rehabilitation, and audiological testing. The minimum length of follow-up should be two years postimplant and a statistically significant number of the patients should be followed for three years.

Investigations of this nature are to be conducted in such a way that the participating subjects or patients are exposed to the least possible risk consistent with the anticipated benefits. Each patient must be advised that an investigational device is being used and informed consent must be executed by the patient. Patient information and consent should follow FDA Guidelines on Informed Consent - 21 CFR Part 50.

The applicant shall state whether the studies were conducted in accordance with the requirements of 21 CFR Part 52 (sponsor/monitor), Part 54 (clinical investigations), Part 56 (institutional review boards), Part 812 or 813 (investigational device exemptions). If, after the effective dates of these parts, any studies were not conducted in compliance with these parts, an explanation of the differences between the procedures followed and those required by these parts shall be included.

A clinical study must be repeated each time a device is changed significantly (i.e., a change that would alter the safety and/or effectiveness of the device) or a new prototype developed, unless waived by the review committee. A new trial is not required for minor modifications, these changes should be incorporated into the current trial.

1. Clinical protocols:

   a. Preimplant assessment

      (1) A complete presurgical medical examination including: a preoperative history, an otologic evaluation with temporal bone radiology (i.e., high resolution CT scan), and whether tinnitus is present, including a definition of tinnitus

      (2) A complete audiological test battery under earphones, i.e., puretone air and bone conduction thresholds for each ear, tolerance levels, acoustic immittance measurements, speech detection thresholds and other communicative measures such as speechreading, environmental sounds, and the MAC battery (The following frequencies should be included for puretone air conduction testing: 250, 500, 1000, 2000, 4000, and 8000 Hz; if there is a positive response at 8000 Hz, test 10,000 and 12,000 Hz).

      (3) Soundfield audiological assessment in both aided and unaided conditions, i.e., warble-tone thresholds (250, 500, 1000, 2000, 4000, and 8000 Hz), tolerance levels, real ear measurements, speech detection thresholds, and communicative tests, e.g., MAC Battery, speechreading, environmental sounds, speech recognition and discrimination

(4) Counseling for each patient, with the use of an interpreter when the patient is knowledgeable in manual communication

(5) Evaluation of communication ability by self and/or others (i.e., clinician, layman) using a numerical rating scale of abilities

(6) Educational assessment/counseling if appropriate to age and ability level

(7) Psychological and/or neuropsychological evaluation of patient

b. Postimplant assessment

(1) Frequency of evaluation, length and frequency of follow-up (including the time course from implant surgery to post-implant tuning)

(2) Counseling (as in preimplant condition)

(3) Psychophysical testing, (e.g., electrode threshold, loudness scaling, electrode pitch ranking)

(4) Electrical measurements for implants with a percutaneous connection

(5) Assessment of device reliability

(6) Speech-processor evaluation (relevant to preimplant protocol, i.e., warbletone thresholds, MCL, speech tests, environmental sounds)

(7) Medical evaluation (see preimplant evaluation)

(8) Complete audiological testing under earphones (see preimplant evaluation)

(9) Soundfield audiological evaluation (see preimplant evaluation)

(10) Educational assessment/counseling if appropriate to age and ability level

(11) Rehabilitation program, including length and frequency of rehabilitation and integration with patient's educational program (if appropriate)

(12) Evaluation of communication ability relevant to preimplant evalaution (e.g., speechreading with and without the processor, speech tracking)

(13) Controlled studies specifying the nature of controls to be used (e.g., comparison to established norms of similar subjects process, single subject repeated design)

2. Number of investigators and subjects per investigation

   a. The investigators should be knowledgeable in the areas of otolaryngology and audiology and be experienced in middle ear surgical procedures.

   b. In addition to a certified otologist, experienced in middle ear surgical procedures, there should be a certified audiologist and speech-language pathologist or aural rehabilitationist on the team.

3. Study population, including the distribution of relevant variables

   a. Concomitant therapy and special education, e.g., hearing aid use, aural habilitation, use of tactile devices

   b. Numbers of patients in experimental and, when used, control groups

   c. Age distribution

   d. Etiology of deafness

   e. Other pertinent variables, e.g., educational history, audiological history, age at onset of deafness (including manner of determining age of onset)

4. Subject selection criteria (including a description of, and rationale for, any deviation from the patient inclusion criteria)

    a. A profound sensorineural hearing impairment (i.e., greater than 90 dB HL) in each ear as determined by objective hearing tests

        (1) Puretone procedures, including the test frequencies: 250, 500, 1000, 2000, 4000, and 8000 Hz; if there is a positive response at 8000 Hz, test 10,000 and 12,000 Hz

        (2) Warbletone procedures, including the test frequencies: 250, 500, 1000, 2000, 4000, and 8000 Hz.

    b. General suitability for implantation including an assessment for intellectual and psychological adequacy

    c. Inability to derive benefit from a strong/high gain hearing aid

    d. No contraindications to placing the electrode array in the cochlea or the receiver/stimulator in the skull (as determined by radiography and/or an equivalent procedure)

    e. No contraindications for undergoing implantation surgery (e.g., absence of cochlea, active infectious process)

    f. Absence of a functioning cochlear implant in either ear (This eliminates bilateral implantation and reimplantation, except for failure of the device.)

5. Study period

6. Safety and effectiveness data

7. Adverse reactions and complications (including a description of each individual adverse reaction and/or complication)

8. Patient discontinuation

9. Patient complaints

10. Device failures and replacements (including complete failure analysis report for each device failure)

11. Tabulations of data from all individual subject report forms

12. Copies of subject report forms for each subject who did not complete the investigation

13. Results of statistical analyses of the clinical investigations (including the statistical methodology and rationale for each test and/or references and/or formulas for each methodology and a description of and explanation for any deviations from the methodology)

    a. In order to determine the effectiveness of the device, this study should include a sufficient number of patients and complete follow-up at regular intervals.

    b. The analysis of the data should be done by the success or failure rate and the complication rate.

14. Contraindications and precautions

    a. The use of cochlear implants is contraindicated in patients in whom deafness is due to lesions of the acoustic nerve or central auditory pathway or the presence of an active infectious process of the middle ear.

    b. Use of cochlear implant is contraindicated in patients whom preoperative radiographic evidence indicates the absence of cochlear development.

15. Any other appropriate information (explain)

    a. A summary table specifying duration of follow-up for each subject in the investigation

    b. A statement as to why a study was discontinued, if it was, or a statement that it is continuing, if such is the case

    c. The methods used to eliminate bias on the part of the subjects or investigators

16. Was this investigation conducted under an IDE and in compliance with 21 CFR Part 812, Investigational Device Exemptions?

VII. One Investigator

Single investigator studies for cochlear implants will not be accepted.

VIII. Reports and Other Information

A. Bibliography of all published reports not submitted under 21 CFR 814.20(b)(6), whether adverse or supportive, that concern the safety and effectiveness of the device

B. Identification, discussion and analysis of any other data, information or report (foreign or domestic) relevant to an

evaluation of the safety and effectiveness of the device

C. Copies of any published report or unpublished information if FDA or an FDA advisory committee requests

IX. Samples

Only if requested by FDA, one or more samples of the device

X. Labeling

A. Submit copies of all proposed labeling. Include instructions for installation and any information, literature, or advertising that constitutes labeling under section 201(m) of the Federal Food, Drug, and Cosmetic Act.

B. Labeling for the device (Draft labeling should be prepared using the following format, order, and section headings: DESCRIPTION,INDICATIONS AND USAGE, INFORMATION FOR USE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE EFFECTS, and where necessary, REFERENCES. If there are not known contraindications, warnings, precautions, or adverse effects, the labeling should indicate "none" or "none known" under each of the headings. The labeling must state whether the device is to be restricted (21 CFR 801 and 899).

1. Labeling must clearly state that the patient will be unable to undergo magnetic resonance imaging (i.e., MRI) after implantation.

2. Labeling should include the benefits and risks of other approved cochlear implant methods and of other recognized communicative methods and devices such as cued speech, hearing aids, and tactile aids.

C. Surgical manual

D. Audiologist manual

E. Patient information

F. Promotional material, written or other, if requested by FDA

XI. Environmental Assessment

A. If claiming a categorical exclusion, information to justify the exclusion

B. An environmental assessment

XII. Other Information

A. Color additive petition (only when applicable)

1. If not included in the PMA, has a color additive petition been submitted to the FDA Center for Food Safety and Applied Nutrition?

2. Included as a separate volume of the PMA

XIII. Appendix

A. Patient informed consent (for cochlear implant studies) must be consistent with 21 CFR Part 50 and should include:

1. A statement describing the device and its functions

2. The possible loss of any residual hearing in the implanted ear as a result of the surgery

3. The benefits and risks of other approved cochlear implant methods and of other recognized communicative methods and devices such as cued speech, hearing aids, and tactile aids

4. The potential risks, as well as the benefits, of cochlear prostheses in general and the risks of the particular type of cochlear implant under evaluation such as a lump behind the ear, electrical or mechanical failure of the device requiring its removal, a numbness or stiffness about the ear, injury to the facial nerve, taste disturbances, perilymph or cerebrospinal fluid leakage, revision/reinsertion, tinnitus, vertigo, infection, blood or fluid collection at the site of surgery, facial twitch, meningitis, recognized potential problems of prolonged anesthesia

5. The possibility that it may be necessary to remove the device and/or utilize other methods in an attempt to regain hearing (include risks of revision/reinsertion)

6. The inability of the patient to undergo magnetic resonance imaging (i.e., MRI) after implantation

7. The potential risk of further degeneration of nerve cells, calcification, bone growth, and long-term effects on the central nervous system

8. A stipulation that the patient should also be advised that he or she must agree to remain in communication with the investigator or the manufacturer, with no time limit, in order that the long-term success or failure of the device may be determined

9. The possibility that stimulation of the auditory nerve could have severe limitations in transmitting speech information

B. Postmarket surveillance

Postmarket surveillance may be needed for cochlear prostheses for a number of reasons.

1. The possibility of defects in the manufacture of a particular "run" or lot of devices, necessitating the location of patients

2. The possibility that hazards during extended use are discovered at some future date

3. The possibility that stimulation of the auditory nerve could have severe limitations in transmitting speech information (long term speech testing is important to assess benefit)

4. The possibility of the corrosion of the electrode

5. The long-term effects on the central nervous system

6. The possibility of adverse effects of electrical stimulation on the function of the auditory nerve fibers

7. The potential for organisms to pass from the skin surface (in the case of percutaneous connections) or from the middle ear to the cochlea which can cause a life-threatening infection

8. The possibility of calcification and new bone formation

9. The possibility of facial twitching

10. The possibility of the influence of the mechanical properties of electrode arrays on implantation performance

In order to locate all the cochlear prostheses, the manufacturer is to keep records of regional distribution and final distribution (e.g., individual clinics or hospitals). In the event of recall or the need to survey the incidence of adverse reactions, the manufacturer will provide this information to the FDA. In addition, the manufacturers will provide FDA with the total number of prostheses distributed yearly. The manufacturer should conduct an adverse reaction reporting system in order to actively solicit adverse reactions from physicians and hospitals. The manufacturer should provide educational information for the use of cochlear implant devices to the physicians and hospitals.